# Clinical trial results:
# A double blind controlled clinical study to investigate the efficacy and tolerability of subcutaneous Treprostinil sodium in patients with severe non-operable Chronic Thromboembolic Pulmonary Hypertension (CTREPH II)

## Summary

| | |
|---|---|
| EudraCT number | 2008-006441-10 |
| Trial protocol | AT CZ SK DE |
| Global end of trial date | |

**Results information**

| | |
|---|---|
| Result version number | v1 (current) |
| This version publication date | 25 April 2018 |
| First version publication date | 25 April 2018 |

## Trial information

**Trial identification**

| | |
|---|---|
| Sponsor protocol code | 116-02 |

**Additional study identifiers**

| | |
|---|---|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT01416636 |
| WHO universal trial number (UTN) | - |

Notes:

**Sponsors**

| | |
|---|---|
| Sponsor organisation name | SciPharm Sàrl |
| Sponsor organisation address | 7, Fausermillen, Mertert, Luxembourg, 6689 |
| Public contact | Clinical Trial Management, SciPharm Sàrl, +43 6649639319, b.tan@scipharm.eu |
| Scientific contact | Clinical Trial Management, SciPharm Sàrl, +43 6649639319, b.tan@scipharm.eu |

Notes:

**Paediatric regulatory details**

| | |
|---|---|
| Is trial part of an agreed paediatric investigation plan (PIP) | No |
| Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial? | No |
| Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial? | No |

Notes:

## Results analysis stage

| | |
|---|---|
| Analysis stage | Interim |
| Date of interim/final analysis | 10 February 2017 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 24 November 2016 |
| Global end of trial reached? | No |

Notes:

## General information about the trial

Main objective of the trial:

To determine the effect of subcutaneous Treprostinil sodium on 6MWT distance after 24 weeks in patients with severe non-operable chronic thromboembolic pulmonary hypertension

Protection of trial subjects:

During their participation in the clinical trial the patients were insured as defined by legal requirements. The compensation of the patient in the event of study-related injuries complied with the applicable regulations.

Each subject had the right to withdraw the study at any timepoint without negative affect on subjects future health care.

The health status of trial subjects was assessed every 6 weeks during the study visits. All adverse events and adverse drug reactions had to be reported in the CRF. In addition, trial subject had to rate infusion site pain on a scale from 0 (no pain) to 10 (very severe pain).
If a subject did not tolerate an increase of the dose due to adverse drug reactions, the dose could be reduced. In the discreation of the investigator the dose was up titrated again after stabilization or recovery of the adverse drug reaction.
Furthermore, in case of deterioration of the underlying disease or the general health status, the subject had to be withdrawn from the study if withdrawal criteria were met.

Background therapy:

Patients were not allowed to receive any prostanoids within 30 days before Screening or be scheduled to receive any prostanoids during the participation in the study.
It was also prohibited to include patients who received any new type of chronic therapy (a different category of vasodilator or diuretic) for PH within 30 days prior to Randomization, except anticoagulants. If a patient received another type of vasodilator for PH for more than 30 days prior to Randomization the medication should be kept on stable doses throughout the blinded phase of its study participation.

Evidence for comparator:

Based on published clinical data (Skoro-Sajer, 2007) the CTREPH 116-02 trial was designed as a prospective randomized double-blind controlled study comparing high dose sc. Treprostinil (target dose ~ 30 ng/kg/min.) with low dose sc. Treprostinil (target dose ~ 3 ng/kg/min). A classical placebo controlled design was considered not feasible due to the characteristic smell of the Treprostinil solution and the anticipated local side reactions induced by subcutaneously administered Treprostinil. However earlier investigations with subcutaneous Treprostinil indicated that infusion site pain is not directly dependent on the rate of dose increase (Skoro-Sajer et al 2008). Therefore, a low dose comparator was determined to facilitate complete double blinding. Furthermore, this approach avoided 6 months placebo treatment of severely sick study participants which might be considered unethical.
The determination of target doses in low and high dose groups was based on published literature and the clinical experience of investigators with the use of Treprostinil in PAH patients, whose risk benefit profile was expected to be similar in the CTEPH population. Long-term data showed a positive outcome of exercise capacity after three years at an average dose of 40ng/kg/min. in PAH and CTEPH patients (Lang et al 2006). A significant increase of long term survival in IPAH patients was observed after one year at an average dose of 26 ng/kg/min. in another analysis (Barst et al 2006). In contrast doses of < 5ng/kg/min. showed no clinical improvement (Simonneau et al 2002).

| | |
|---|---|
| Actual start date of recruitment | 09 March 2009 |
| Long term follow-up planned | Yes |
| Long term follow-up rationale | Safety, Ethical reason |
| Long term follow-up duration | 100 Years |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

## Population of trial subjects

### Subjects enrolled per country

| | |
|---|---|
| Country: Number of subjects enrolled | Poland: 16 |
| Country: Number of subjects enrolled | Austria: 54 |
| Country: Number of subjects enrolled | Czech Republic: 34 |
| Country: Number of subjects enrolled | Germany: 1 |
| Worldwide total number of subjects | 105 |
| EEA total number of subjects | 105 |

Notes:

### Subjects enrolled per age group

| | |
|---|---|
| In utero | 0 |
| Preterm newborn - gestational age < 37 wk | 0 |
| Newborns (0-27 days) | 0 |
| Infants and toddlers (28 days-23 months) | 0 |
| Children (2-11 years) | 0 |
| Adolescents (12-17 years) | 0 |
| Adults (18-64 years) | 42 |
| From 65 to 84 years | 62 |
| 85 years and over | 1 |

## Subject disposition

### Recruitment

Recruitment details:

First patient was enrolled on March 9, 2009 and the last patient completed the study on November 24, 2016.
Recruitment of subjects was performed continously in all participating study centres.
Recruitment for the study was stopped due to planned interim analysis and restarted afterwards.

### Pre-assignment

Screening details:

The selection of patients was performed according to inclusion and exclusion criteria defined in the study protocol CTREPH 116-02.
138 patients were assesed for eligibility, 33 did not qualify for enrollment (e.g. operable CTEPH, no consent given).
105 patients qualified for enrollment.

### Period 1

| | |
|---|---|
| Period 1 title | blinded phase (overall period) |
| Is this the baseline period? | Yes |
| Allocation method | Randomised - controlled |
| Blinding used | Double blind |
| Roles blinded | Investigator, Monitor, Subject |

Blinding implementation details:

For this clinical trial Treprostinil sodium was used in the strengths of 1 mg/ml, 2.5 mg/ml, 5 mg/ml and 10 mg/ml. The drug was administered subcutaneously by an infusion pump.
The dose differences in the two groups (low dose & high dose) were induced due to the different strengths of Treprostinil vials. This means that patients in both arms always used the same infusion rates for the subcutaneous infusion pumps.

### Arms

| | |
|---|---|
| Are arms mutually exclusive? | Yes |
| **Arm title** | low dose |

Arm description:

Dose was titrated to a target dose of 3ng/kg/min. Due to the predefined infusion rate setting schedule and the handling requirements of the infusion pump an interim dose of up to 6 ng/kg/min could be reached for few days at the end of the periods 1,2 and 3. This depended on the patient’s exact weight and is caused by the limited infusion rate setting possibility of the infusion pump.

| | |
|---|---|
| Arm type | Active comparator |
| Investigational medicinal product name | Treprostinil sodium |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for infusion |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

The drug was administered subcutaneously by an infusion pump. Dose was titrated to a target dose of 3ng/kg/min. Due to the predefined infusion rate setting schedule and the handling requirements of the infusion pump an interim dose of up to 6 ng/kg/min could be reached for few days at the end of the periods 1,2 and 3. This depended on the patient’s exact weight and is caused by the limited infusion rate setting possibility of the infusion pump.

The medication was provided in 20ml glas vials filled with 10ml solution for infusion. The vials for patients in the low dose group contained only solution with a dosage of 1mg/ml of Treprostinil sodium.

| | |
|---|---|
| **Arm title** | high dose |

Arm description:

Dose were titrated to a target dose of 30ng/kg/min. Due to the predefined infusion rate setting schedule a dose of up to 33 ng/kg/min. could be reached.

| | |
|---|---|
| Arm type | Experimental |

| | |
|---|---|
| Investigational medicinal product name | Treprostinil sodium |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for infusion |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

The drug was administered subcutaneously by an infusion pump. Dose were titrated to a target dose of 30ng/kg/min. Due to the predefined infusion rate setting schedule a dose of up to 33 ng/kg/min. could be reached.

The medication was provided in 20ml glas vials filled with 10ml solution for infusion. The vials for patients in the high dose group contained solutions with a dosage of 1mg/ml, 2.5mg/ml, 5mg/ml and 10mg/ml of Treprostinil sodium. The strengths of the vials for the high dose group were raised continuously during the first 12 weeks (Period I – 1 mg/ml; Period II – 2.5 mg/ml; Period III – 5 mg/ml; Period IV-VIII – 10mg/ml).

| **Number of subjects in period 1** | low dose | high dose |
|---|---|---|
| Started | 52 | 53 |
| Termination Visit | 46 | 45 |
| Completed | 46 | 45 |
| Not completed | 6 | 8 |
| Adverse event, serious fatal | 1 | 2 |
| Adverse event, non-fatal | 3 | 1 |
| progression of concomitant disease | - | 2 |
| Lack of efficacy | 2 | 3 |

## Baseline characteristics

| Reporting groups | |
|---|---|
| Reporting group title | low dose |
| Reporting group description: | |
| Dose was titrated to a target dose of 3ng/kg/min. Due to the predefined infusion rate setting schedule and the handling requirements of the infusion pump an interim dose of up to 6 ng/kg/min could be reached for few days at the end of the periods 1,2 and 3. This depended on the patient's exact weight and is caused by the limited infusion rate setting possibility of the infusion pump. | |
| Reporting group title | high dose |
| Reporting group description: | |
| Dose were titrated to a target dose of 30ng/kg/min. Due to the predefined infusion rate setting schedule a dose of up to 33 ng/kg/min. could be reached. | |

| Reporting group values | low dose | high dose | Total |
|---|---|---|---|
| Number of subjects | 52 | 53 | 105 |
| Age categorical | | | |
| Units: Subjects | | | |
| Adults (18-64 years) | 27 | 15 | 42 |
| From 65-84 years | 25 | 37 | 62 |
| 85 years and over | 0 | 1 | 1 |
| Age continuous | | | |
| Units: years | | | |
| arithmetic mean | 60.58 | 68.06 | |
| standard deviation | ± 14.59 | ± 11.16 | - |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 30 | 19 | 49 |
| Male | 22 | 34 | 56 |
| WHO NYHA functional class | | | |
| Units: Subjects | | | |
| Class II | 3 | 3 | 6 |
| Class III | 44 | 47 | 91 |
| Class IV | 5 | 3 | 8 |
| 6MWD (6-Minute Walking Distance) | | | |
| Units: meter | | | |
| arithmetic mean | 299.13 | 307.66 | |
| standard deviation | ± 85.7 | ± 68.77 | - |
| Borg Dyspnoea Score | | | |
| Scale from 0-11 | | | |
| Units: 0-11 | | | |
| arithmetic mean | 5.19 | 4.77 | |
| standard deviation | ± 2.25 | ± 2.05 | - |
| Minnesota Living with Heart Failure Questionnaire | | | |
| There were 21 items to be scored between 0 and 5 (0=no / 5=very much)<br>A score sum was calculated for each patient and visits Baseline, week 12 and week 24. | | | |
| Units: 0-105 | | | |
| arithmetic mean | 45.79 | 42.32 | |
| standard deviation | ± 23.16 | ± 21.16 | - |
| pro-BNP | | | |

| | | | |
|---|---|---|---|
| Units: pg/ml | | | |
| arithmetic mean | 2040.29 | 2300.98 | |
| standard deviation | ± 1650.63 | ± 2624.4 | - |
| mPAP (mean Pulmonary Arterial Pressure) | | | |
| Units: mmHg | | | |
| arithmetic mean | 49.77 | 49.92 | |
| standard deviation | ± 10.79 | ± 12.35 | - |
| PVR (Pulmonary Vascular Resistance) | | | |
| Units: dyn.s.cm^-5 | | | |
| arithmetic mean | 809.01 | 845.11 | |
| standard deviation | ± 296.67 | ± 385.5 | - |
| CO (Cardiac Output) | | | |
| Units: L/min | | | |
| arithmetic mean | 4.36 | 4.28 | |
| standard deviation | ± 1.35 | ± 1.32 | - |
| CI (Cardiac Index) | | | |
| Units: L/min/m² | | | |
| arithmetic mean | 2.28 | 2.25 | |
| standard deviation | ± 0.64 | ± 0.67 | - |
| mRAP (mean Risght Artrial Pressure) | | | |
| Units: mmHg | | | |
| arithmetic mean | 10.25 | 9.7 | |
| standard deviation | ± 5.55 | ± 5.99 | - |
| mPCWP (mean Pulmonary Capillary Wedge Pressure) | | | |
| Units: mmHg | | | |
| arithmetic mean | 9.53 | 10.42 | |
| standard deviation | ± 4.3 | ± 4.87 | - |

## End points

### End points reporting groups

| | |
|---|---|
| Reporting group title | low dose |

Reporting group description:

Dose was titrated to a target dose of 3ng/kg/min. Due to the predefined infusion rate setting schedule and the handling requirements of the infusion pump an interim dose of up to 6 ng/kg/min could be reached for few days at the end of the periods 1,2 and 3. This depended on the patient's exact weight and is caused by the limited infusion rate setting possibility of the infusion pump.

| | |
|---|---|
| Reporting group title | high dose |

Reporting group description:

Dose were titrated to a target dose of 30ng/kg/min. Due to the predefined infusion rate setting schedule a dose of up to 33 ng/kg/min. could be reached.

### Primary: Change in 6MWT distance

| | |
|---|---|
| End point title | Change in 6MWT distance |

End point description:

| | |
|---|---|
| End point type | Primary |

End point timeframe:

6MWT distance was assessed at baseline and termination

| End point values | low dose | high dose | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 52[1] | 53[2] | | |
| Units: meter | | | | |
| arithmetic mean (standard deviation) | 3.83 (± 56.21) | 45.43 (± 71.29) | | |

Notes:

[1] - Missing values at termination were imputed by LOCF

[2] - Missing values at termination were imputed by LOCF

| | |
|---|---|
| **Attachments (see zip file)** | primary efficacy endpoint/primary efficacy endpoint.jpg |

### Statistical analyses

| | |
|---|---|
| **Statistical analysis title** | analysis of change in 6MWT |

Statistical analysis description:

The pooled data of both stages were also evaluated using an ANCOVA model resulting in a two-sided p-value of 0.002 (0.001 one-sided), so also significantly in favour of the high dose group.
As the normality assumption of the ANCOVA model residuals was rejected (p value < 0.0001), the pooled stage I and stage II data were additionally analysed using the Mann-Whitney U test with a two-sided p value of 0.0003 (0.00015 one-sided) for the dose effect.

| | |
|---|---|
| Comparison groups | low dose v high dose |

| | |
|---|---|
| Number of subjects included in analysis | 105 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.003 |
| Method | Wilcoxon (Mann-Whitney) |

## Secondary: Change in 6MWT distance after 12 weeks

| | |
|---|---|
| End point title | Change in 6MWT distance after 12 weeks |
| End point description: baseline value compared to 6MWT distance after 12 weeks | |
| End point type | Secondary |
| End point timeframe: baseline vs. 12 weeks | |

| End point values | low dose | high dose | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 52[3] | 53[4] | | |
| Units: meter | | | | |
| arithmetic mean (standard deviation) | 27.31 (± 57.29) | 32.7 (± 63.45) | | |

Notes:

[3] - Missing values at week 12 were imputed by LOCF

[4] - Missing values at week 12 were imputed by LOCF

### Statistical analyses

| Statistical analysis title | analysis of change in 6MWT after 12 weeks |
|---|---|
| Comparison groups | low dose v high dose |
| Number of subjects included in analysis | 105 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.27 [5] |
| Method | Wilcoxon (Mann-Whitney) |

Notes:

[5] - The ANCOVA model resulted in a two-sided p-value of 0.71 (0.355 one-sided). As the normality assumption of the ANCOVA model residuals was rejected (p value < 0.0001), the analysis after 12 weeks was additionally performed using Mann-Whitney U-test.

## Secondary: Change in WHO NYHA functional class

| | |
|---|---|
| End point title | Change in WHO NYHA functional class |
| End point description: Change in WHO NYHA functional class was compared between baseline and termination | |
| End point type | Secondary |
| End point timeframe: baseline vs. termination | |

| End point values | low dose | high dose | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 52 | 53 | | |
| Units: subjects | | | | |
| improved | 9 | 27 | | |
| no change | 36 | 22 | | |
| worse | 3 | 2 | | |
| not done | 4 | 2 | | |

**Statistical analyses**

| Statistical analysis title | analysis of change in WHO NYHA FC |
|---|---|
| Comparison groups | low dose v high dose |
| Number of subjects included in analysis | 105 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0019 [6] |
| Method | Chi-squared |

Notes:

[6] - Additional evaluation was performed using Fisher Exact test resulting in a p-value of 0.0012

**Secondary: Change in Borg Dyspnoe Score**

| End point title | Change in Borg Dyspnoe Score |
|---|---|
| End point description: | |
| Change in BDS Score (0-11) was compared between baseline and termination | |
| End point type | Secondary |
| End point timeframe: | |
| baseline vs. termination | |

| End point values | low dose | high dose | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 48 | 48 | | |
| Units: 0-11 | | | | |
| arithmetic mean (standard deviation) | 0.13 (± 2.43) | 0.44 (± 2.21) | | |

**Statistical analyses**

| Statistical analysis title | analysis of change in Borg Dyspnoea Score |
|---|---|
| Comparison groups | low dose v high dose |

| | |
|---|---|
| Number of subjects included in analysis | 96 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.307 |
| Method | Wilcoxon (Mann-Whitney) |

## Secondary: Change in Minnesota Living with Heart Failure Questionnaire

| | |
|---|---|
| End point title | Change in Minnesota Living with Heart Failure Questionnaire |

End point description:

Change in Quality of Life assessed with the Minnesota Living with Heart Failure Questionnaire was compared between baseline and termination. A sore sum was calculated for each patient and visit baseline and termination.

| | |
|---|---|
| End point type | Secondary |

End point timeframe:

baseline vs. termination

| **End point values** | low dose | high dose | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 46 | 50 | | |
| Units: 0-105 | | | | |
| arithmetic mean (standard deviation) | -4.63 (± 19.34) | -6.36 (± 22.9) | | |

### Statistical analyses

| **Statistical analysis title** | analysis of change in MQoL |
|---|---|
| Comparison groups | low dose v high dose |
| Number of subjects included in analysis | 96 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.557 |
| Method | Wilcoxon (Mann-Whitney) |

## Secondary: Clinical Worsening

| | |
|---|---|
| End point title | Clinical Worsening |

End point description:

Clinical worsening was defined as:

- Decrease of 6MWD from Baseline of more than 20%
- Decrease of NYHA functional class from Baseline
- Hospitalization due to CTEPH with the need of additional PH specific treatment (need of additional diuretic therapy was also rated as PH specific treatment)
- Death due to CTEPH

| End point type | Secondary |
|---|---|
| End point timeframe:<br>whole study duration | |

| **End point values** | low dose | high dose | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 52 | 53 | | |
| Units: subjects | | | | |
| Hospitalization due to CTEPH worsening | 6 | 4 | | |
| Death due to CTEPH worsening | 0 | 2 | | |
| Reduction of 6MWD < 20% compared to baseline | 7 | 2 | | |
| Worsening of WHO NYHA functional class | 4 | 2 | | |
| At least one finding of Clinical Worsening | 12 | 7 | | |

### Statistical analyses

| **Statistical analysis title** | analysis of Clinical Worsening |
|---|---|
| Comparison groups | low dose v high dose |
| Number of subjects included in analysis | 105 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.214 [7] |
| Method | Fisher exact |

Notes:

[7] - P-value given is the result of the "at least one finding of clinical worsening" category as this was the main analysis.

### Secondary: change in pro-BNP levels

| End point title | change in pro-BNP levels |
|---|---|
| End point description:<br>The individual perecentage change in pro-BNP level were assessed between baseline and termination. | |
| End point type | Secondary |
| End point timeframe:<br>baseline vs. termination | |

| **End point values** | low dose | high dose | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 46 | 46 | | |
| Units: pg/ml | | | | |
| arithmetic mean (standard deviation) | 41.68 (± 104.2) | 0.84 (± 63.32) | | |

**Statistical analyses**

| **Statistical analysis title** | analysis of change in pro-BNP level |
|---|---|
| Statistical analysis description:<br>individual percentage change in pro-BNP level were assessed using Mann-Whitney U-test. | |
| Comparison groups | low dose v high dose |
| Number of subjects included in analysis | 92 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.032 |
| Method | Wilcoxon (Mann-Whitney) |

| **Secondary: Change in mPAP** | |
|---|---|
| End point title | Change in mPAP |
| End point description: | |
| End point type | Secondary |
| End point timeframe:<br>change in mPAP between baseline and termination | |

| **End point values** | low dose | high dose | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 47 | 47 | | |
| Units: mmHg | | | | |
| arithmetic mean (standard deviation) | -0.4 (± 6.87) | -3.36 (± 8.04) | | |

**Statistical analyses**

| **Statistical analysis title** | analysis of change in mPAP |
|---|---|
| Comparison groups | low dose v high dose |
| Number of subjects included in analysis | 94 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.04 |
| Method | Wilcoxon (Mann-Whitney) |

## Secondary: Change in PVR

| End point title | Change in PVR |
|---|---|

End point description:

| End point type | Secondary |
|---|---|

End point timeframe:
change in PVR between baseline and termination

| End point values | low dose | high dose | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 47 | 48 | | |
| Units: dyn.s.cm^-5 | | | | |
| arithmetic mean (standard deviation) | 72.96 (± 284.95) | -214.23 (± 324.28) | | |

### Statistical analyses

| Statistical analysis title | analysis of change in PVR |
|---|---|
| Comparison groups | low dose v high dose |
| Number of subjects included in analysis | 95 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 |
| Method | Wilcoxon (Mann-Whitney) |

## Secondary: change in CO

| End point title | change in CO |
|---|---|

End point description:

| End point type | Secondary |
|---|---|

End point timeframe:
change in CO between baseline and termination

| End point values | low dose | high dose | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 47 | 48 | | |
| Units: L/min | | | | |
| arithmetic mean (standard deviation) | -0.22 (± 1.06) | 0.63 (± 1.47) | | |

**Statistical analyses**

| Statistical analysis title | analysis of change in CO |
|---|---|
| Comparison groups | low dose v high dose |
| Number of subjects included in analysis | 95 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 |
| Method | Wilcoxon (Mann-Whitney) |

**Secondary: change in CI**

| End point title | change in CI |
|---|---|

End point description:

| End point type | Secondary |
|---|---|

End point timeframe:

change in CI between baseline and termination

| End point values | low dose | high dose | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 47 | 48 | | |
| Units: L/min/m² | | | | |
| arithmetic mean (standard deviation) | -0.16 (± 0.54) | 0.42 (± 0.9) | | |

**Statistical analyses**

| Statistical analysis title | analysis of change in CI |
|---|---|
| Comparison groups | low dose v high dose |
| Number of subjects included in analysis | 95 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 |
| Method | Wilcoxon (Mann-Whitney) |

## Secondary: change in mRAP

| End point title | change in mRAP |
|---|---|

End point description:

| End point type | Secondary |
|---|---|

End point timeframe:
change in mRAP between baseline and termination

| **End point values** | low dose | high dose | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 47 | 48 | | |
| Units: mmHg | | | | |
| arithmetic mean (standard deviation) | 2.87 (± 6.82) | 0.65 (± 5.08) | | |

### Statistical analyses

| **Statistical analysis title** | analysis of change in mRAP |
|---|---|
| Comparison groups | low dose v high dose |
| Number of subjects included in analysis | 95 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.227 |
| Method | Wilcoxon (Mann-Whitney) |

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

AE and ADR were assessed regularly during the study visists every 6 weeks. The investigator had the possibility to contact the patient in between the visist to follow up on adverse events as well as the patient could contact the study team at any time.

Adverse event reporting additional description:

Patients were asked if new adverse events developed since the last study visit. All adverse events and adverse drug reactions had to be documented in source documents and in the CRF. It had to be assessed if the event was related to the study drug by the investigator.

| | |
|---|---|
| Assessment type | Systematic |

### Dictionary used

| | |
|---|---|
| Dictionary name | MedDRA |
| Dictionary version | 19.0 |

### Reporting groups

| | |
|---|---|
| Reporting group title | safety population |

Reporting group description:

Safety population:
The safety population accounts for 105 patients (all patients randomized with post Baseline safety data).

| **Serious adverse events** | safety population | | |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 19 / 105 (18.10%) | | |
| number of deaths (all causes) | 3 | | |
| number of deaths resulting from adverse events | 3 | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Polycythaemia vera | | | |
| subjects affected / exposed | 1 / 105 (0.95%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Vascular disorders | | | |
| Aortic stenosis | | | |
| subjects affected / exposed | 1 / 105 (0.95%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Haematoma | | | |
| subjects affected / exposed | 1 / 105 (0.95%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

| | | | | |
|---|---|---|---|---|
| Worsening of Pulmonary Hypertension | | | | |
| subjects affected / exposed | 2 / 105 (1.90%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 1 | | | |
| Cardiac disorders | | | | |
| Cardiac failure | | | | |
| subjects affected / exposed | 2 / 105 (1.90%) | | | |
| occurrences causally related to treatment / all | 0 / 3 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Dyspnoea | | | | |
| subjects affected / exposed | 1 / 105 (0.95%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Right ventricular failure | | | | |
| subjects affected / exposed | 5 / 105 (4.76%) | | | |
| occurrences causally related to treatment / all | 0 / 7 | | | |
| deaths causally related to treatment / all | 0 / 1 | | | |
| Syncope | | | | |
| subjects affected / exposed | 1 / 105 (0.95%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Nervous system disorders | | | | |
| Syncope | | | | |
| subjects affected / exposed | 1 / 105 (0.95%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| General disorders and administration site conditions | | | | |
| General physical health deterioration | | | | |
| subjects affected / exposed | 1 / 105 (0.95%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Incarcerated hernia | | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 105 (0.95%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gastrointestinal disorders | | | |
| Diarrhoea | | | |
| subjects affected / exposed | 1 / 105 (0.95%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Nausea | | | |
| subjects affected / exposed | 1 / 105 (0.95%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Haemoptysis | | | |
| subjects affected / exposed | 1 / 105 (0.95%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Renal and urinary disorders | | | |
| Acute kidney injury | | | |
| subjects affected / exposed | 1 / 105 (0.95%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Infections and infestations | | | |
| Appendicitis | | | |
| subjects affected / exposed | 1 / 105 (0.95%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Escherichia bacteraemia | | | |
| subjects affected / exposed | 1 / 105 (0.95%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Sepsis | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 105 (0.95%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Metabolism and nutrition disorders | | | |
| Hypokalaemia | | | |
| subjects affected / exposed | 1 / 105 (0.95%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

Frequency threshold for reporting non-serious adverse events: 5 %

| **Non-serious adverse events** | safety population | | |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 104 / 105 (99.05%) | | |
| Vascular disorders | | | |
| Worsening of Pulmonary Hypertension | | | |
| subjects affected / exposed | 13 / 105 (12.38%) | | |
| occurrences (all) | 14 | | |
| Cardiac disorders | | | |
| Oedema peripheral | | | |
| subjects affected / exposed | 17 / 105 (16.19%) | | |
| occurrences (all) | 21 | | |
| Right ventricular failure | | | |
| subjects affected / exposed | 6 / 105 (5.71%) | | |
| occurrences (all) | 8 | | |
| Nervous system disorders | | | |
| Headache | | | |
| subjects affected / exposed | 16 / 105 (15.24%) | | |
| occurrences (all) | 19 | | |
| General disorders and administration site conditions | | | |
| Decreased appetite | | | |
| subjects affected / exposed | 7 / 105 (6.67%) | | |
| occurrences (all) | 7 | | |
| Flushing | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed<br>occurrences (all)<br><br>Infusion site erythema<br>subjects affected / exposed<br>occurrences (all)<br><br>Infusion site pain<br>subjects affected / exposed<br>occurrences (all)<br><br>Infusion site pruritus<br>subjects affected / exposed<br>occurrences (all)<br><br>Infusion site swelling<br>subjects affected / exposed<br>occurrences (all) | 8 / 105 (7.62%)<br>9<br><br>38 / 105 (36.19%)<br>42<br><br>81 / 105 (77.14%)<br>96<br><br>10 / 105 (9.52%)<br>10<br><br>7 / 105 (6.67%)<br>7 | | |
| Gastrointestinal disorders<br>Diarrhoea<br>subjects affected / exposed<br>occurrences (all)<br><br>Nausea<br>subjects affected / exposed<br>occurrences (all)<br><br>Vomiting<br>subjects affected / exposed<br>occurrences (all) | <br><br>46 / 105 (43.81%)<br>51<br><br>8 / 105 (7.62%)<br>10<br><br>6 / 105 (5.71%)<br>8 | | |
| Respiratory, thoracic and mediastinal disorders<br>Cough<br>subjects affected / exposed<br>occurrences (all) | <br><br>7 / 105 (6.67%)<br>7 | | |
| Skin and subcutaneous tissue disorders<br>Pruritus<br>subjects affected / exposed<br>occurrences (all) | <br><br>6 / 105 (5.71%)<br>7 | | |
| Musculoskeletal and connective tissue disorders<br>Arthralgia<br>subjects affected / exposed<br>occurrences (all) | <br><br>6 / 105 (5.71%)<br>6 | | |

| | | | |
|---|---|---|---|
| Pain in extremity<br>subjects affected / exposed<br>occurrences (all) | 12 / 105 (11.43%)<br>14 | | |
| Infections and infestations<br>Nasopharyngitis<br>subjects affected / exposed<br>occurrences (all) | 14 / 105 (13.33%)<br>15 | | |
| Metabolism and nutrition disorders<br>Hypokalaemia<br>subjects affected / exposed<br>occurrences (all) | 9 / 105 (8.57%)<br>11 | | |

## More information

## Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|---|---|
| 17 March 2009 | Protocol version 3.0 was submitted and approved before the initiation of the study and inclusion of the first patient.<br>1) Exclusion criteria: The intake of phosphodiesterase inhibitors (PDEIs) before and/or during the study participation was not any more prohibited. In patients receiving stable doses of PDEIs but still fulfilling all inclusion and exclusion criteria the concomitant medication is not expected to impact the study outcome or interfere with the study drug. In addition, it would not have been possible to reach sample size with only including treatment naïve patients because of the rareness of the disease. From an ethical point of view, it would not be possible to stop any treatments the patient received prior to the inclusion into the study.<br>2) Questionnaire: Camphor Questionnaire was replaced by Minnesota Living With Heart Failure Questionnaire (MLHFQ) because it was identified as more appropriate for the evaluation of the study outcome and the fulfilling of requirements for the clinical trial.<br>3) Observational efficacy assessments: The percentage of patients showing clinical improvement at the end of study was added as an observational endpoint. |
| 11 May 2009 | Protocol version 4.0, 19.03.2009<br>1) Change of the sponsor: The CTREPH 116-02 trial was initiated by Univ. Prof. Dr. Irene Lang, Medical University of Vienna in 2008 as an investigator initiated trial. In order to facilitate the achievement of the predefined sample size it was necessary to recruit patients in study centres in different countries. However, the Medical University of Vienna was not able to take over the sponsorship of a multinational/multicentre trial therefore the sponsorship for the non-commercial clinical trial was assigned to Medical Research Network GmbH.<br>2) Right heart catheterization: The period prior to inclusion from which results from right heart catheterization of the patient could be accepted to serve as reference for the proof of inclusion and exclusion criteria was prolonged from three to six months. |
| 23 September 2009 | Protocol version 5.0, 27.08.2009<br>1) Exclusion criteria: Serious liver problems (Child-Pugh, class C), such as active gastrointestinal ulcer, intrabdominal haemorrhaging were added as exclusion criteria.<br>2) Hospitalization: The possibility to hospitalize patients for carrying out the Baseline examinations or to specify the training with the delivery system was added to the protocol. |
| 21 May 2010 | Protocol version 6.0, 21.04.2010<br>1) Control dose: The information, that interim doses of up to 5 ng/kg/min. could temporarily be reached in the low dose group between Baseline and week 12, was added to the protocol. This could not be prevented as all patients need to follow the same up-titration schedule (depending on their weight) in order to guarantee blinding. Furthermore, the infusion pump only allows dose adaptations of a minimum of 0.002 ml/h. This could also lead to very slight dose variations which neither impact study outcome nor patients' safety.<br>2) Stopping rules, withdrawal criteria and procedures: A passage about the criteria which could lead to premature termination of the clinical trial was added.<br>3) Blinding: Following request from the German authorities a chapter describing the blinding and randomization procedures was added. |
| 10 December 2010 | Protocol version 7.0, 19.10.2010<br>1) Safety evaluations: A procedure of monitoring infusion site pain during study participation was added in order to have a better overview about the occurrence of infusion site pain. The intensity of infusion site pain since last visit was assessed at each scheduled visit using a visual analogue scale (VAS) (1-10) which had to be completed by the investigator according to the patient's survey. |

| | |
|---|---|
| 12 December 2011 | Protocol version 8.0, 22.11.2011<br>1) Blood chemistry: The parameter Bicarbonate/CO2 was deleted due to missing medicinal relevance for CTEPH.<br>2) Coagulation times: The parameter PTT was added due to recommendation of the investigators. |
| 16 January 2013 | version 10.0, 30.11.2012<br>1) Sponsor: Sponsorship was transferred from MRN-Medical Research Network GmbH to SciPharm Sàrl.<br>2) Genetic sub-study: Genetic sub-study was not continued.<br>3) Secondary objectives/endpoints: The criteria for clinical worsening were adapted according to internationally established approaches. Additionally, to the Borg score the heart rate and the oxygen saturation measurement during 6MWT were added as secondary endpoints.<br>4) Exploratory objectives/endpoints: BNP and ADMA measurements and percentage of patients with clinical improvement were deleted as endpoints. The hemodynamic parameters to be evaluated were clearly defined and analysis of signs and symptoms of the CTEPH was added.<br>5) Safety objectives/endpoints: Safety evaluations were adapted according to the international guidelines.<br>6) Proof of non-operability assessment: A clearly defined evaluation process of the non-operability assessment of the patients was established<br>7) Satellite centres: A process for including patients from foreign centres (not able to serve as study centres by their own) was defined. ( This procedure was never established and is therefore not further explained in the CSR)<br>8) Inclusion criteria: Adjusted to guarantee a proper selection with regard to the safety of the patients and the validity of data according to the GCP guideline.<br>9) Exclusion criteria: Adjusted to guarantee a proper selection with regard to the safety of the patients and the validity of data according to the GCP guideline.<br>10)Withdrawal criteria: Withdrawal criteria were defined and properly described. In the previous protocol versions, the withdrawal criteria were not specified in detail and explained in different sections of the protocol.<br>was noch? AUSMISTEN! |
| 15 May 2013 | Protocol version 11.0, 12.03.2013<br>1) Follow-up phase: A follow-up open label extension phase was added to the protocol in order to give the patient the possibility to be treated with Treprostinil sodium after finishing 24 weeks of the randomized, double-blinded phase of the clinical trial.<br>2) Screening: It was added to the protocol that examinations which were already performed within 7 days prior to the Screening visit did not necessarily had to be repeated if the investigator considered that the results were still appropriate (e.g. laboratory testing, spirometry).<br>3) Visit 3 & Visit 5: Under exceptional circumstances Visit 3 and Visit 5 could be performed by a phone call. It gave the patient the option to still participate in the study even though he/she was not able to come to the scheduled date of Visit 3 or Visit 5.<br>4) Visit 4: A procedure was implemented if patient was not able to come to the visit on the scheduled date. |
| 04 December 2014 | Protocol version 12.0, 23.10.2014<br>Following significant adaptations were included to the new protocol version:<br>1) Biostatistician: Biostatistician was changed.<br>2) Inclusion criteria: In order to follow the advice of medical experts it was defined that in case of recurrent PH after PEA, test results from before the surgery were acceptable if a typical specimen was harvested during PEA substantiating the diagnosis of CTEPH.<br>3) Right heart catheterization: The measurement of SVR was deleted because the parameter was identified as not specific for CTEPH.<br>4) Coagulation times: The measurement PT and PTT were deleted because the INR measurement is sufficient for monitoring the coagulation.<br>5) Sample size recalculation: Based on the results of the interim analysis it was decided to continue the study and proceed with the originally planned sample size for stage II of n=23 per treatment group.<br>6) Efficacy analysis: The statistical methods have been explained according to the expert review report from the medical University of Vienna. |

| | |
|---|---|
| 12 November 2015 | Protocol version 13.0, 29.09.2015<br>1) Biostatistician: Biostatistician was changed as the Medical University of Vienna could not fulfil all requirements of a commercial trial.<br>2) Treatment compliance: The defined compliance of 80-120% was changed to ≥ 80%.<br>3) Intention to treat population: Data cleaning committee was implemented in order to decide about the validity of evaluation of the data after the end of trial.<br>4) Sample size recalculation for stage II: It was defined that also data of the patients who did not reach the final visit were qualified for the analysis. |
| 09 February 2017 | Protocol version 14.0, 12.01.2017<br>1) Efficacy assessments: In course of discussions with the consulting statistician it was decided not to evaluate the time to clinical worsening (in the blinded study phase) but only comparing the number of cases in the two different dosage groups. Since clinical worsening parameters were only assessed in course of planned visits or hospitalizations the number of measurements would not provide valid results for a time-to clinical worsening assessment.<br>2) Intention to treat population: It was redefined that intention to treat set comprises all patients randomized who received at least one dose of study medication.<br>The redefinition was done to comply with the "Full Analysis Set" as described in "International Conference on Harmonisation; Guidance on Statistical Principles for Clinical Trials".<br>3) Per protocol population: As a result of the adaption of the ITT population it was redefined that the per protocol set comprises all patients from the full analysis set for whom valid data were available.<br>The data cleaning committee decides about the validity of specific data for the per-protocol analysis.<br>4) Modified per protocol: Because after redefining the ITT and PP populations a modified per protocol was not relevant anymore.<br>5) Efficacy analysis: It was defined that in case the data are not normally distributed and/or the homogeneity of variances could not be assumed, non-parametric testing is performed (Wilcoxon-Mann-Whitney U- test) to ensure correctness and validity of the study results. |

Notes:

## Interruptions (globally)

Were there any global interruptions to the trial? Yes

| Date | Interruption | Restart date |
|---|---|---|
| 15 April 2012 | Recruitment for the study was stopped due to planned interim analysis.<br>As the result of the interim analyses led to continuation of the study recruitment was restarted again. | 20 February 2013 |

Notes:

## Limitations and caveats

None reported